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Hemodynamic and Metabolic Basis of Impaired Exercise Tolerance in Patients With Severe Left Ventricular Dysfunction

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Hemodynamic and metabolic changes were measured at rest and during exercise in 23 patients with chronic heart failure and in 6 control subjects. Exercise was limited by leg fatigue in both groups and capacity was 40% lower in the patients with failure. At rest, comparing patients with control subjects, heart rate and right atrial and pulmonary wedge pressure were higher; cardiac output, stroke volume and work indexes and ejection fraction were lower; mean arterial and right atrial pressure and systemic resistance were similar. During all phases of exercise in patients with heart failure, pulmonary wedge pressure and systemic vascular resistance were higher and pulmonary vascular resistance remained markedly elevated compared with values in control subjects. Cardiac output was lower in the patients with failure, but appeared to have the same physiologic distribution in both groups during exercise.

Although arterial-femoral venous oxygen content difference was higher in patients with heart failure, this increase did not compensate for the reduced blood flow. Even though the maximal oxygen consumption was significantly reduced, femoral venous lactate and pH values were higher than values in control subjects, but femoral venous pH was similar in both groups at their respective levels of maximal exercise. Ejection fraction was lower in those with heart failure at rest and did not increase with exercise. Ventilation in relation to oxygen consumption was higher in patients with failure than in control subjects. In patients with failure, although wedge pressure and pulmonary vascular resistance are high, exercise is limited mainly by fatigue due to acidosis and reduced leg blood flow in exercising muscle.

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In normal subjects and athletes, exercise is limited by fatigue thought to be due to metabolic changes that occur in working muscles (1,2). During exercise in patients with chronic heart failure, abnormal hemodynamics and pulmonary gas exchange patterns develop (3–5), but the mechanism by which these result in impaired exercise tolerance remains unclear. The purpose of this study was to determine the hemodynamic and metabolic factors that limit exercise in patients with heart failure.

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Methods

Study patients. Twenty-three men (mean age 51 years, range 27 to 62) with chronic heart failure (New York Heart Association functional class II or III) were studied. The mean left ventricular ejection fraction at rest on contrast ventriculography was 24% (range 14% to 43%). Heart failure was caused by previous myocardial infarction in 10 patients and dilated cardiomyopathy in 13. No patient had valvular disease, and all were in sinus rhythm. Primary pulmonary disease was excluded by history, and normal lung function was measured by spirometry and expiratory flow rates (6). All patients were taking diuretic drugs, seven were receiving digoxin and three were taking a vasodilator. No medication was taken on the morning of the study.

Six men (mean age 48 years, range 43 to 55) who had angiographically normal left ventricular function (mean ejection fraction at rest 63%) and coronary arteries constituted a control group. All six had undergone cardiac catheterization because of atypical chest pain.

Informed consent, was obtained from all subjects. The

study protocol was approved by the Ethics Review Committee of the hospital.

Exercise protocol. Subjects were positioned on a semiupright (45°) electronically braked ergometer (Siemens Elema model 380B). After measurements were taken at rest, patients began exercising at an initial work load of 15 W with the pedal speed maintained at 60 rpm. The work load was increased by 15 W every 3 min until symptoms or exhaustion prevented further exercise (maximal work load). During exercise, a CM_5 electrocardiographic (ECG) lead was monitored continuously, and a 12 lead ECG was recorded every minute.

Hemodynamic measurements. A 7F Swan-Ganz thermodilution catheter was inserted to record right atrial, pulmonary artery and pulmonary wedge pressures. Systemic arterial pressure was recorded through a radial artery cannula. The zero reference point for pressures was set at the fourth intercostal space in the mid-axillary line. Cardiac output was measured in triplicate by the thermodilution technique with use of an analog computer system (model 701, Instrumentation Laboratory). At rest and during the last 2 min of each exercise level, stroke volume, stroke work index and systemic vascular resistance were calculated by standard formulas (7).

A 6F Goodale-lubin catheter was inserted into the right femoral vein and advanced proximally under fluoroscopic control to lie just proximal to the anterior pelvic brim in the anteroposterior projection. In this position, the catheter tip was well away from the insertion of the internal iliac vein.

Radionuclide ventriculography. Gated radionuclide ventriculography was performed in a modified left anterior oblique projection simultaneously with the rest of the observations at rest and exercise. Red blood cells were labeled in vivo with 25 mCi of technetium-99m. Count data were collected using a single crystal gamma camera (Sigma 420, Technicare Ohio) fitted with a slant-hole high sensitivity collimator, and interfaced to a digital computer system (PDP 11/34A Digital). Radionuclide data were analyzed by a semiautomatic edge detection program, as described previously (8). Left ventricular ejection fraction was measured by a count-based method validated in this laboratory against the values obtained from contrast angiography (9).

Metabolic measurements. Blood samples were drawn simultaneously from the radial artery, pulmonary artery (mixed venous) and femoral vein at rest and during the last 10 s of each exercise level. Five milliliters was immediately lysed in ice-cold perchloric acid solution for the enzymatic estimation (DuPont ACA) of systemic arterial and femoral venous lactate levels, and another 5 ml was used for hemoglobin concentration and blood gas analysis, including oxygen saturation, bicarbonate (HCO_3^-) and pH. Blood gas tensions were measured with use of a Corning 175 Blood Gas Analyzer. Oxygen saturation was obtained from the measured partial pressure of oxygen (Po_2), corrected for pH, partial pressure of carbon dioxide (Pco_2) and temperature. Hemoglobin content was measured spectrophoretically with an Instrumentation Laboratory CO_2 oximeter. The accuracy obtained by using the Corning blood/gas analyzer to calculate oxygen saturation from measurements of oxygen, Pco_2, pH and temperature was confirmed in a study that compared oxygen saturation derived from blood gas tension analysis and the oxygen saturation measured by chemical means using a Van Slyke manometric apparatus.

Arterial-mixed venous oxygen content difference was calculated as arterial(a)-mixed venous(v) oxygen content difference = 1.39 × (radial aSo_2 − pulmonary aSo_2) × hemoglobin concentration, where S = saturation. Arterial-femoral venous oxygen content difference was calculated as arterial-femoral venous oxygen content difference = 1.39 × (radial aSo_2 − femoral vSo_2) × hemoglobin concentration (10).

Ventilation was measured at rest and during exercise using a low resistance two-way valve (Hans-Rudolph 2700, dead space 90 ml). The expired air was passed through a heated pneumotachograph (Hewlett-Packard), which was calibrated daily. Mixed expired air was sampled at a constant rate and analyzed for oxygen using an Applied Electrochemistry S-3A analyzer, and for carbon dioxide using an infrared Datex analyzer (Godart). Calibration of these instruments was carried out using cylinders of known gas mixtures that had been prepared gravimetrically and checked for accuracy. Minute ventilation and mixed expired oxygen and carbon dioxide were measured at rest and during the last minute of each exercise level, and oxygen consumption (Vo_2) and carbon dioxide production (Vco_2) were calculated. The respiratory exchange ratio (R value) was derived from the ratio Vco_2/Vo_2; excess carbon dioxide production was calculated as $Vco_2 - 0.75Vo_2$ (11).

Statistical analysis. Results are expressed as mean values ± SEM. Student's *t* test was used to compare the difference between patients and normal subjects at rest and at maximal exercise. The relation between exercise response and work load was determined by regression analysis. To test the difference in response of each variable between patients and normal subjects, the slopes and intercepts of the regression lines were compared using an analysis of covariance (12). A significant difference was achieved when the F ratio resulted in a p value of <0.05. Comparisons of nonlinear relations were done after logarithm transformation of the data.

Results

Exercise tolerance and symptoms. The mean maximal work load achieved was 125 ± 7 W for control subjects and 75 ± 5 W for patients with chronic heart failure ($p < 0.001$).

JACC Vol. 15, No. 5
April 1990:986–94

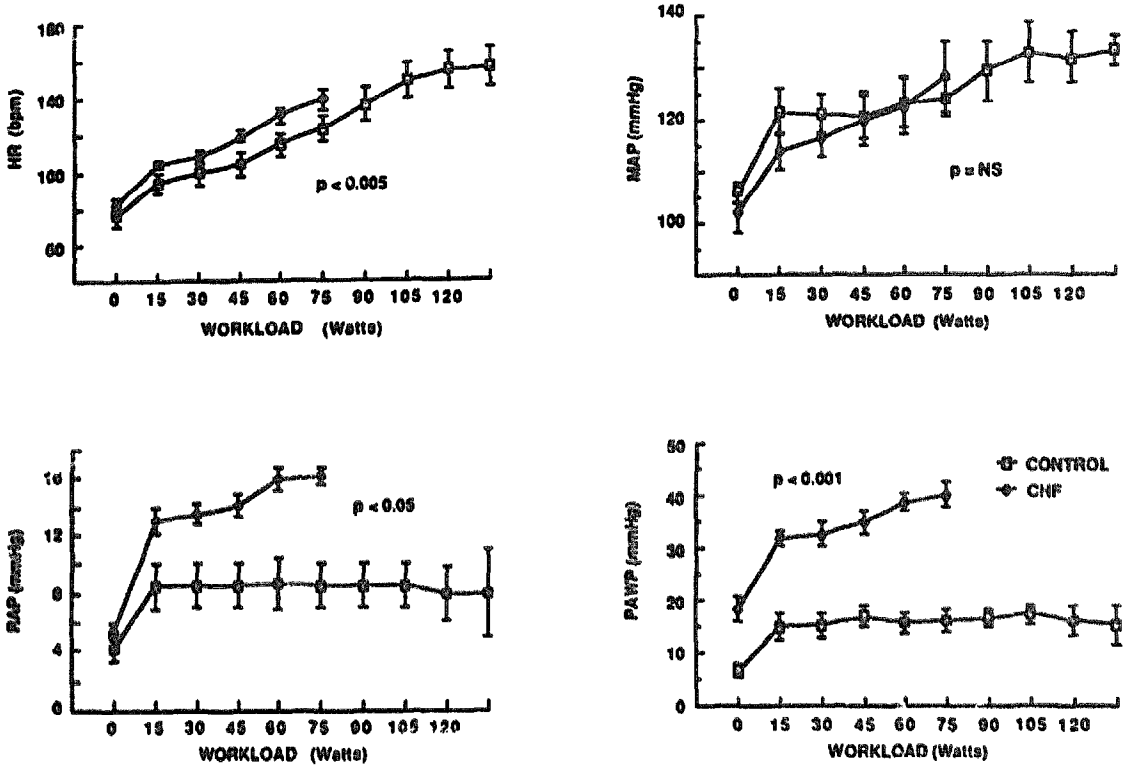


Figure 1. Heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP) and pulmonary artery wedge pressure (PAWP) at rest and during exercise in the control and the congestive heart failure (CHF) groups. Probability (p) values are based on the differences during exercise at identical work loads (that is, the work loads of the patients with heart failure compared with the same work load in control subjects).

Table 1. Hemodynamic Measurements at Rest and at Maximal Exercise in the Control and Heart Failure Groups (mean values ± SEM)

	Control Subjects		Patients With CHF	
	Rest	Wmax	Rest	Wmax
HR (beats/min)	76 ± 5	161 ± 7	82 ± 3	139 ± 5‡
MAP (mm Hg)	106 ± 2	137 ± 5	102 ± 4	125 ± 5
RAP (mm Hg)	5 ± 1	9 ± 2	9 ± 1	16 ± 1‡
PAWP (mm Hg)	7 ± 1	17 ± 2	19 ± 2†	38 ± 3‡
SVI (ml/m^2)	35 ± 3	56 ± 4	27 ± 2*	36 ± 3‡
SWI (g·m·m^{-2})	48 ± 4	91 ± 8	32 ± 4†	42 ± 4‡
CO (liters/min)	5.0 ± 0.7	16.4 ± 0.7	4.3 ± 0.3	9.5 ± 0.7‡
LVEF (%)	63 ± 3	73 ± 3	25 ± 3‡	23 ± 3‡
PVR (dyne·s·cm^{-5})	128 ± 16	74.4 ± 11.2	200 ± 24†	192 ± 24‡
SVR (dyne·s·cm^{-5})	1,753 ± 164	629 ± 33	1,878 ± 144	970 ± 72*

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ versus control subjects at rest or maximal exercise. CHF = congestive heart failure; CO = cardiac output; HR = heart rate; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PAWP = pulmonary wedge pressure; RAP = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index; Wmax = maximal work load.

Data presented reflect the maximal level attained by each group. Although the patients became breathless, they stopped because of fatigue and not dyspnea. No patient developed angina or ischemic ST segment changes during exercise.

Hemodynamic data

At rest (Table 1). When patients with heart failure were compared with control subjects, pulmonary wedge pressure (Fig. 1) and resistance were significantly higher (Fig. 2). Stroke volume, stroke work index and ejection fraction were significantly lower (Fig. 3). Heart rate, mean arterial and right atrial pressures (Fig. 1) cardiac output (Fig. 4) and systemic vascular resistance (Fig. 2) were not significantly different.

At maximal work (Table 1). Heart rate, cardiac output (Fig. 4), ejection fraction, stroke work and stroke volume indexes were lower (Fig. 3). Right atrial and pulmonary wedge pressures (Fig. 1) and systemic and pulmonary resistance (Fig. 2) were higher.

During exercise (Table 2). Cardiac output (Fig. 4), stroke volume, stroke work index and ejection fraction (Fig. 3) were significantly lower. Mean arterial pressure was not significantly different (Fig. 1). Although systemic vascular resistance decreased to nearly half of its value at rest in the patients with heart failure, it remained significantly higher than it did in control subjects (Fig. 2). Pulmonary vascular

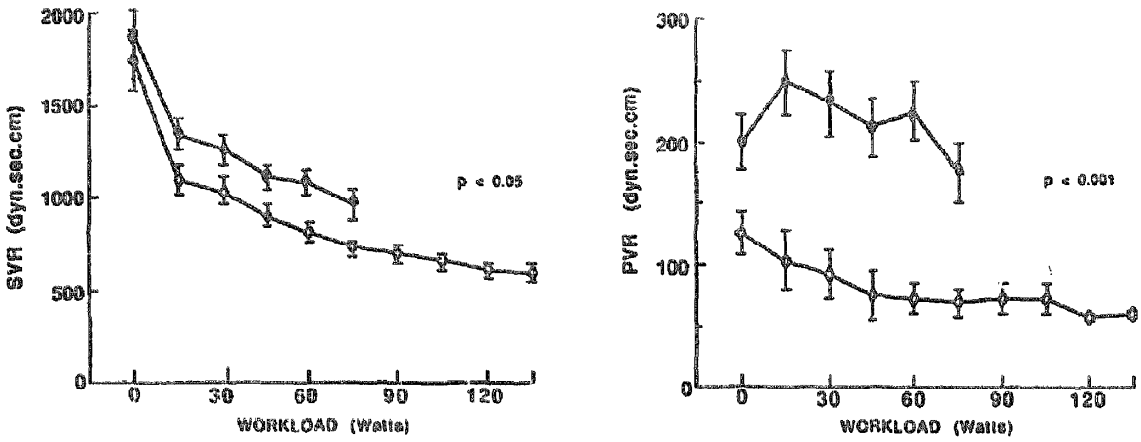


Figure 2. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) at rest and during exercise in the control (○) and heart failure (CHF) (●) groups; p values as in Figure 1.

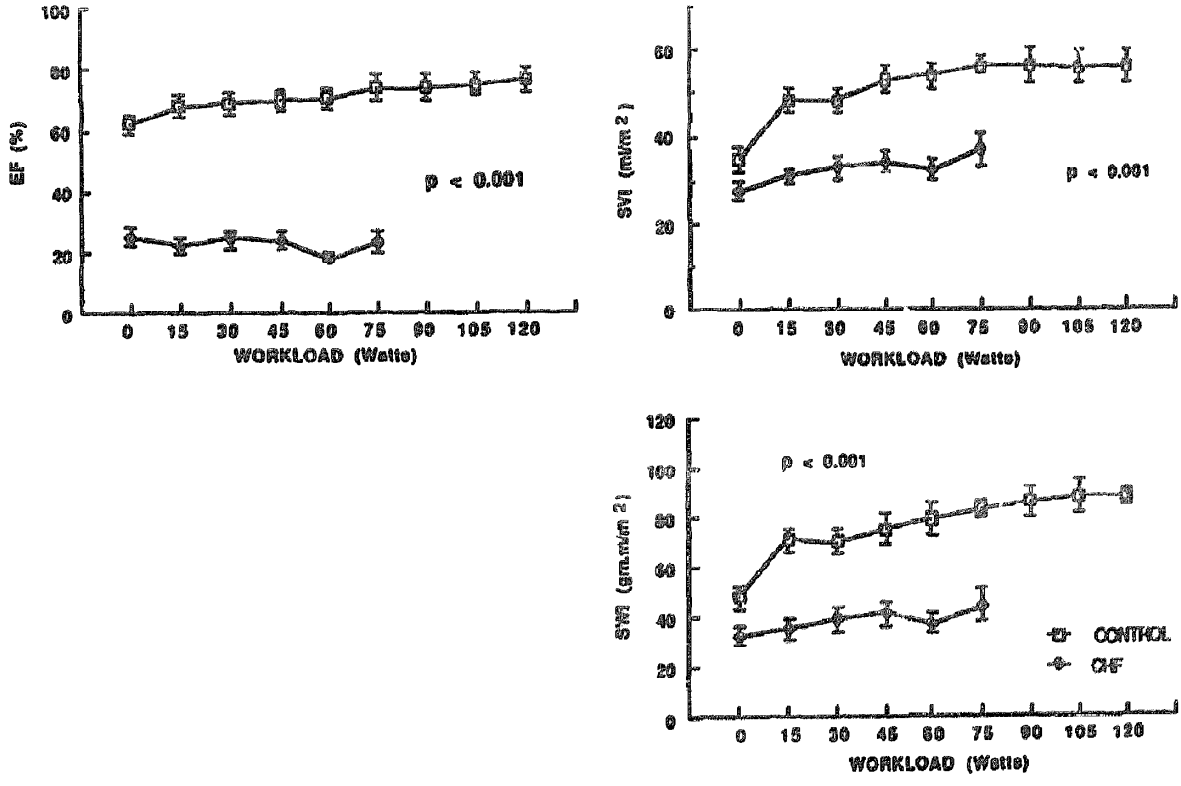
resistance decreased from rest to exercise in the control subjects, but in patients with heart failure it remained consistently high and close to the value observed at rest (Fig. 2).

Metabolic Data

At rest (Table 3). In the patients with heart failure, mixed venous and femoral venous oxygen saturation and femoral venous Po_2 were significantly lower and the femoral-arterial venous oxygen content difference was significantly higher than values in control subjects.

At maximal exercise (Table 3). The maximal exercise capacity of the patients with heart failure was 60% of that of the control subjects.

Figure 3. Left ventricular ejection fraction (EF), stroke volume index (SVI) and stroke work index (SWI) at rest and during exercise in the control (○) and heart failure (CHF) (●) groups; p values as in Figure 1.



JACC Vol. 15, No. 5
April 1990:986–94

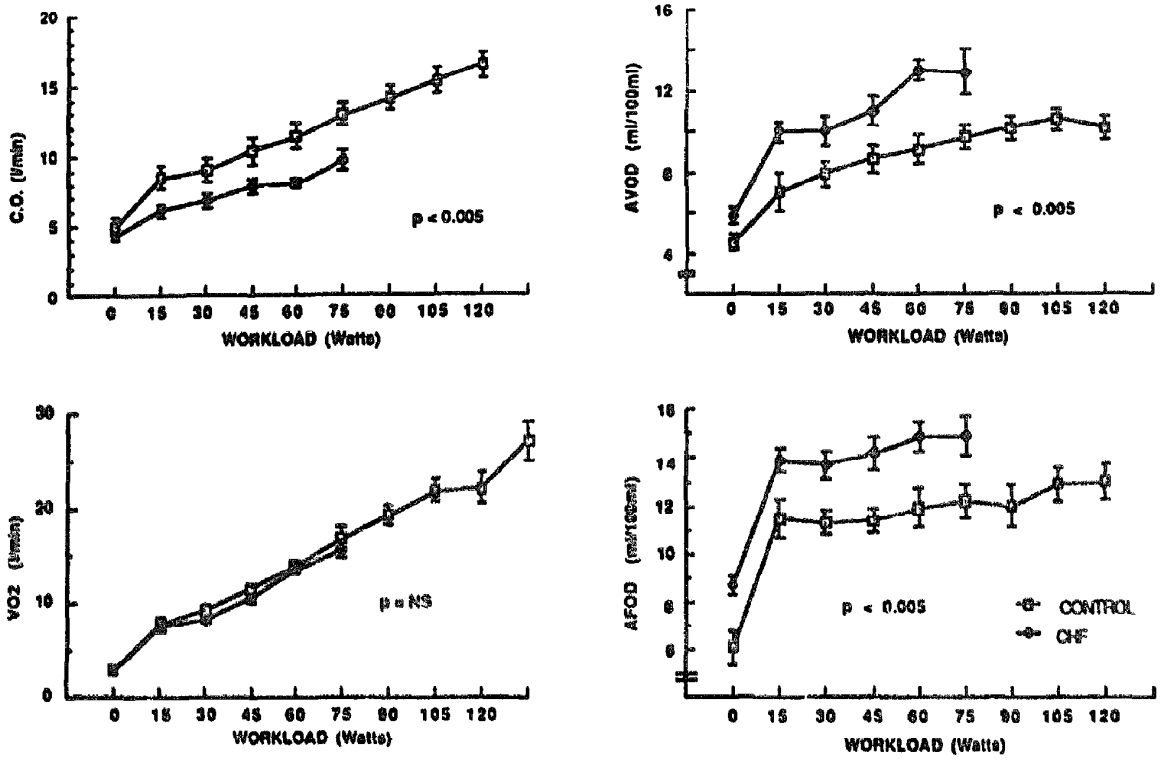


Figure 4. Cardiac output (C.O.), arterial-mixed venous oxygen content difference (AVOD), oxygen consumption (Vo_2) and arterial-femoral venous oxygen content difference (AFOD) at rest and during exercise in the control (□) and heart failure (CHF) (●) groups; p values as in Figure 1.

Arterial. In the patients with heart failure, arterial pH was lower and was associated with lower systemic arterial lactate levels than values in the control subjects ($p < 0.001$). Mixed venous oxygen saturation and Po_2 were also lower. Values for Pco_2, and pH and arterial-mixed venous oxygen content difference were similar in both groups.

Femoral vein. Femoral venous oxygen saturation, Po_2 and lactate levels were lower in the patients with heart failure, but values for venous Pco_2, pH and arterial-femoral venous oxygen content difference were similar in both groups.

Gas exchange. Minute ventilation (VE) and oxygen consumption (Vo_2) were significantly lower in the patients with heart failure. Carbon dioxide production, ventilation exchange ratio and excess carbon dioxide values were not significantly different in the two groups.

During exercise. Mixed venous arterial pH (Fig. 5) was higher during but not at maximal exercise in patients with heart failure.

Table 2. Changes in Exercise Hemodynamics (Y) Related to Progressive Increase in Work Loads (watts) (X) in the Control and Heart Failure Groups

	Regression Equation and Correlation Coefficient				p Value	
	Control Subjects		Patients With CHF		Slope	Intercept
HR (beats/min)	Y = 0.84X + 6.27;	r = 0.88	Y = 0.07X + 4.59;	r = 0.80		<0.001
MAP (mm Hg)	Y = 0.28X + 102;	r = 0.56	Y = 0.27X + 102;	r = 0.51		
RAP (mm Hg)	Y = 0.02X + 6.8;	r = 0.22	Y = 0.11X + 8.9;	r = 0.61	<0.001	<0.001
PAWP (mm Hg)	Y = 0.05X + 12;	r = 0.37	Y = 0.19X + 23;	r = 0.48	<0.001	<0.01
SVI (ml/m^2)	Y = 0.14X + 43;	r = 0.49	Y = 0.14X + 28;	r = 0.44		<0.01
SWI (g·m·m^{-2})	Y = 0.27X + 60;	r = 0.66	Y = 0.19X + 31;	r = 0.38		<0.001
CO (liters/min)	Y = 0.08X + 6.27;	r = 0.88	Y = 0.07X + 4.59;	r = 0.80		<0.01
SVR (dyne·s·cm^{-5})	Y = 6.9X + 1,349;	r = −0.87	Y = 10.6X + 1,624;	r = −0.66		
LVEF (%)	Y = 0.10X + 65;	r = 0.49	Y = 0.03X + 22;	r = 0.10		<0.01

Abbreviations as in Table 1.

Table 3. Metabolic Measurements at Rest and During Maximal Exercise in the Control and Heart Failure Groups (mean values ± SEM)

	Control Subjects		Patients with CHF	
	Rest	Wmax	Rest	Wmax
Systemic artery				
SO_2 (%)	97 ± 0.2	97 ± 0.2	97 ± 0.2	96 ± 0.6
PO_2 (mm Hg)	97 ± 4	98 ± 3	96 ± 3	89 ± 4
PCO_2 (mm Hg)	43 ± 1	38 ± 1	41 ± 1	37 ± 1
pH (unit)	7.40 ± 0.1	7.35 ± 0.01	7.42 ± 0.1	7.39 ± 0.01*
Lactate (mmol/liter)	0.74 ± 0.11	6.69 ± 1.2	0.57 ± 0.08	3.79 ± 0.39†
Pulmonary artery (mixed venous)				
SO_2 (%)	75 ± 2	44 ± 3	60 ± 2†	32 ± 3*
PO_2 (mm Hg)	41 ± 1	28 ± 1	36 ± 1	22 ± 1†
PCO_2 (mm Hg)	47 ± 1	55 ± 2	46 ± 1	56 ± 2
pH (unit)	7.38 ± 0.1	7.22 ± 0.02	7.39 ± 0.1	7.22 ± 0.02
AVOD (ml%)	5 ± 0.4	11 ± 0.5	6 ± 0.4	13 ± 0.5
Femoral vein				
SO_2 (%)	67 ± 3	32 ± 3	53 ± 2‡	19 ± 2‡
PO_2 (mm Hg)	37 ± 2	24 ± 1	29 ± 1‡	17 ± 1‡
PCO_2 (mm Hg)	48 ± 1	63 ± 2	49 ± 1	65 ± 2
pH (unit)	7.37 ± 0.01	7.22 ± 0.02	7.38 ± 0.01	7.25 ± 0.02
Lactate (mmol/liter)	0.63 ± 0.12	7.43 ± 1.3	0.73 ± 0.08	4.27 ± 0.45*
AFOD (ml%)	6.1 ± 0.7	13.6 ± 0.7	8.7 ± 0.4†	15.2 ± 0.6
Pulmonary gas exchange				
VE (liters/min)	7.6 ± 1.1	62.3 ± 3.3	9.9 ± 0.6	43.4 ± 2.7†
VO_2 (ml/min)	225 ± 29	1816 ± 97	255 ± 16	1073 ± 67‡
VCO_2 (ml/min)	182 ± 25	1860 ± 97	280 ± 13	1133 ± 83
R value (unit)	0.8 ± 0.02	1.02 ± 0.02	0.8 ± 0.03	1.07 ± 0.02
$ExsCO_2$ (ml)	13 ± 6	498 ± 37	17 ± 9	328 ± 58

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ versus control subjects at rest or maximal exercise. AFOD = arterial-femoral venous oxygen content difference; AVOD = arterial-mixed venous oxygen content difference; $ExsCO_2$ = excess carbon dioxide production; PCO_2 = carbon dioxide tension; PO_2 = oxygen tension; R = ventilation exchange ratio; SO_2 = systemic oxygen saturation; VCO_2 = carbon dioxide production; VE = minute ventilation; VO_2 = oxygen consumption. Other abbreviations as in Table 1.

Arterial. Mixed venous oxygen content difference (Fig. 6) was higher than oxygen saturation and Po_2 in patients with heart failure.

Femoral vein. Oxygen saturation and Po_2 were lower (Table 4), pH and Pco_2 were lower and lactate was higher in patients with heart failure.

Gas exchange. Minute ventilation, ventilation exchange ratio and excess carbon dioxide were higher in patients with heart failure.

Summary of findings. Ventilatory response to exercise was greater, ventilation in relation to oxygen consumption was increased at the higher work loads and the ventilatory equivalent was abnormal in patients with heart failure. Despite the higher ventilation in the patients with heart failure, arterial Pco_2 values were within normal limits and there was no alveolar hyperventilation.

Discussion

Although the study patients had clinical heart failure and a low ejection fraction, most were in stable condition on diuretic therapy and had a milder grade of heart failure than that in most comparable studies (4,5). Exercise capacity showed abnormal hemodynamic responses, decreased oxygen utilization, increased anaerobic metabolism and reduced exercise capacity compared with that in control subjects. Although dyspnea occurred at maximal exertion, patients stated that fatigue was the main limiting factor; although this response was subjective, it was also consistent.

Hemodynamic changes during exercise. At rest, systemic vascular resistance was comparable in both groups, and decreased during exercise but remained significantly higher in the patients with heart failure (Fig. 2). In contrast, pulmonary vascular resistance was higher at rest in patients with heart failure, and did not decrease with exercise as it did in control subjects (Fig. 2). The rapid and sustained increase in pulmonary wedge pressure during exercise and the high and unaltered pulmonary vascular resistance in patients with heart failure have been reported by others (5), but the differences between pulmonary and systemic resistance changes have not been emphasized and compared previously.

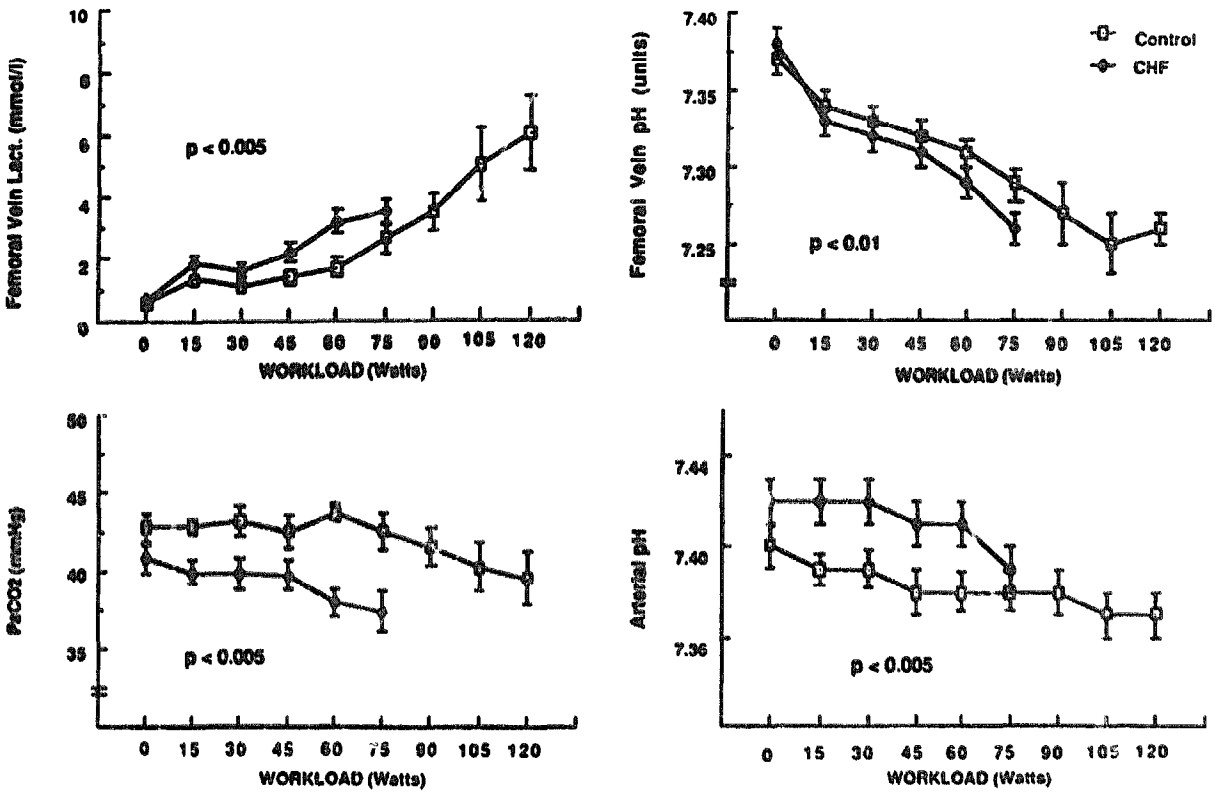


Figure 5. Femoral venous lactate (Lact.), femoral venous pH, arterial carbon dioxide tension ($PaCO_2$) and arterial pH at rest and during exercise in the control (□) and heart failure (CHF) (●) groups; p values as in Figure 1.

Figure 6. Minute ventilation (VE), pulmonary carbon dioxide production (VCO_2), excess carbon dioxide production (Excess CO_2) and pulmonary respiratory exchange ratio (R value) at rest and during exercise in the control (□) and heart failure (CHF) (●) groups; p values as in Figure 1.

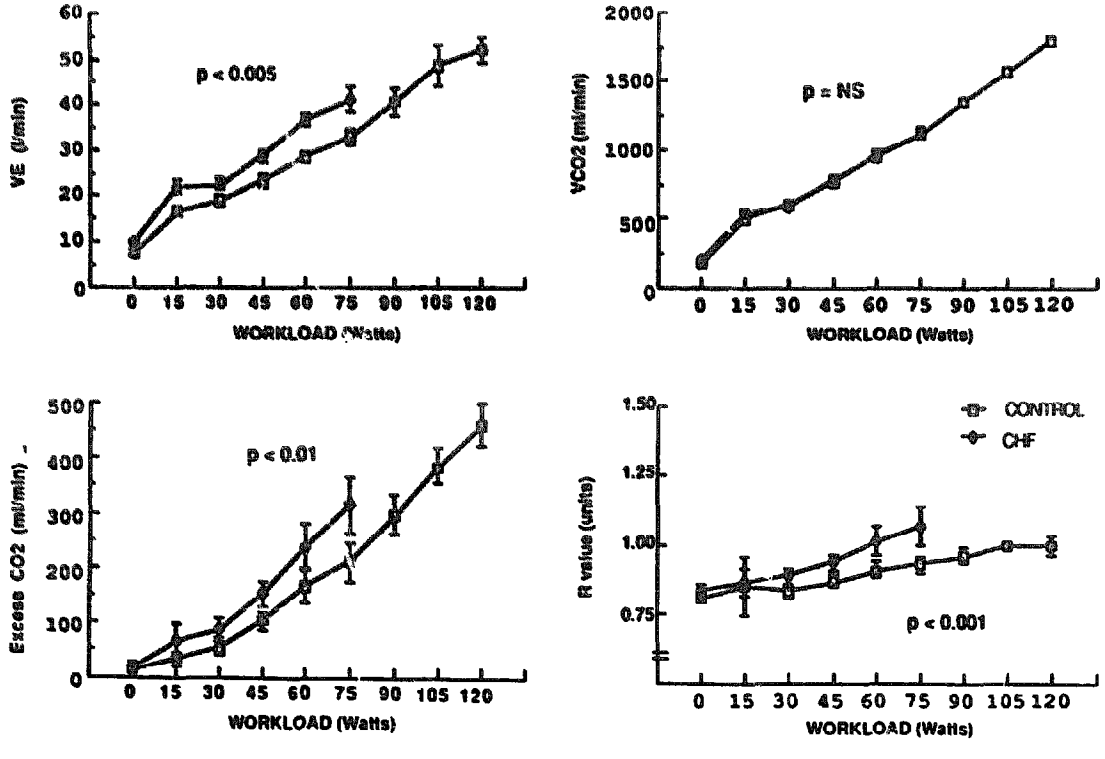


Table 4. Metabolic Measurements (Y) Related to Progressive Increase in Work Loads (X) in the Control and Heart Failure Groups

	Regression Equation and Correlation Coefficient				p Value	
	Control Subjects		Patients With CHF		Slope	Inter
Pulmonary artery (mixed venous)						
SO_2	Y = −0.2X + 68;	r = −0.78	Y = −0.35X + 57;	r = −0.68	<0.05	<0.001
PCO_2	Y = 0.08X + 37;	r = −0.72	Y = −0.13X + 32;	r = −0.51	<0.05	<0.001
pH	Y = −0.009X + 7.4;	r = −0.79	Y = 0.001X + 7.4;	r = −0.63		
AVOD	Y = 0.042X + 6.0;	r = 0.77	Y = 0.067X + 7.8;	r = 0.68	<0.01	<0.01
Femoral vein						
SO_2	Y = −0.17X + 52;	r = −0.63	Y = −0.30X + 40;	r = −0.68	<0.05	<0.001
PO_2	Y = −0.05X + 30;	r = −0.51	Y = −0.11X + 24;	r = −0.54	<0.05	<0.001
PCO_2	Y = 0.09X + 54;	r = 0.70	Y = 0.17X + 52;	r = 0.71	<0.01	<0.05
pH	Y = −0.001X + 7.3;	r = −0.82	Y = −0.002X + 7.4;	r = −0.84	<0.01	<0.01
Lactate	Y = 0.009X − 0.26;	r = 0.88	Y = 0.008X − 0.09;	r = 0.72		<0.01
AFOD	Y = 0.037X + 9.1;	r = 0.62	Y = 0.062X + 11.0;	r = 0.59	<0.05	<0.001
Pulmonary gas exchanges						
VE	Y = 0.38X + 7.49;	r = 0.97	Y = 0.40X + 11.9;	r = 0.75		<0.01
VO_2	Y = 11.2X + 376;	r = 0.90	Y = 8.92X + 403;	r = 0.75		
VCO_2	Y = 13X + 200;	r = 0.99	Y = 12X + 254;	r = 0.96		
r value	Y = 0.002X + 0.8;	r = 0.59	Y = 0.004X + 0.8;	r = 0.59	<0.01	<0.001
$ExsCO_2$	Y = 0.01X + 1.5;	r = 0.89	Y = 0.013X + 1.5;	r = 0.82	<0.05	<0.01

Abbreviations as in Table 1.

Ventilatory and metabolic changes during exercise: role of dyspnea versus fatigue. As exercise progressed, there was no difference in central (pulmonary artery) pH between patients and normal subjects, but there was a lower femoral venous pH when patients and control subjects stopped with fatigue at maximal exercise. Femoral venous pH values were similar, suggesting that acidosis was a common factor that limited exercise in both groups even though the exercise capacity of patients with heart failure and control subjects differed.

During exercise, ventilation was higher in patients with heart failure. Although dyspnea increased progressively with exercise in both groups, it was not the limiting factor. Weber et al. (13) have shown that during exercise, patients with heart failure use only a small proportion of their predicted maximal voluntary ventilation; their finding is in agreement with our data.

When oxygen uptake, cardiac output and arteriovenous oxygen content differences centrally and in the femoral vein were compared at rest and during exercise, the relative arteriovenous oxygen content difference between the legs and the pulmonary artery did not change in patients with heart failure. This finding suggests that in patients with heart failure, blood flow is physiologically distributed during exercise (that is, there is an increased flow to exercising muscle). This observation is in agreement with previous studies (14).

The femoral venous Po_2 did not decrease below the critical level of 10 mm Hg (15,16), suggesting that muscle fatigue is not determined solely by oxygen delivery. Some blood from tissues other than exercising muscle could have been present in our samples, but previous studies (17) have shown that blood flow in skin in patients with heart failure does not contribute significantly to femoral blood flow.

Previous studies. Wilson et al. (18) reported that intramuscular lactate and acidosis may not be responsible for muscular fatigue. However, they did not measure femoral vein lactate and pH as in our study, which demonstrated a different pattern between central and peripheral venous pH. The increased lactate and Vco_2 resulting from exercising muscle is thought to produce hyperpnea in patients with heart failure (18,19), and total ventilation was higher.

Several recent studies (20,21) using nuclear magnetic resonance imaging, have shown consistent abnormalities of metabolism in peripheral muscles in patients with heart failure. It is not clear whether these changes are due to heart failure or to muscular atrophy and disuse that accompany it.

Conclusions. In patients with heart failure, the wide femoral arterial-mixed venous oxygen content difference suggests that blood flow in the leg was reduced during exercise as a result of the low cardiac output plus an inability to further redistribute this to exercising limbs. Both oxygen delivery and utilization in exercising muscles were reduced, and anaerobic metabolism was increased. Despite the elevated pulmonary vascular resistance during exercise observed in patients with heart failure compared with control subjects, fatigue rather than dyspnea limited exercise. Metabolic acids accumulating from the exercising muscles and their effects peripherally appear to be a major factor that limits exercise capacity in patients with heart failure.

JACC Vol. 15, No. 5
April 1990:986–94

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